DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 02/04/10. Claims 40 and 42-52 are currently pending in the application, with claims 1-39 and 41 having being cancelled. Accordingly, claims 40 and 42-52 are being examined on the merits herein.

Receipt of the aforementioned amended claims and Information Disclosure Statement (IDS) is acknowledged and has been entered.

1. Applicant's argument the cited art does not teach the basic concept of treating cystic fibrosis by administering an antidepressant by inhalation has been fully considered. Applicant further argues that newly added claim 47 specifically excludes additional active ingredients and the Ni et al. reference requires the combination of an active ingredient of formula I. Such arguments are not found persuasive as applicant is arguing not previously recited. It is noted that the features upon which applicant relies (i.e., claim 47) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, the Examiner respectfully points out that claim 47 contains the term "comprising" and thus does not exclude additional ingredients. As recited, claim 47 requires the presence of a carrier and a pharmaceutically active component that is an

antidepressant selected from the group consisting of tricyclic and tetracyclic antidepressants. Contrary to applicant's belief, such language as recited does not exclude the presence of other active ingredients but rather renders the claims vague an indefinite. As for the Ni et al. reference, it was provided to demonstrate that the instant claims are obvious in view of the disclosure. Specifically, Ni et al. teach the use of compounds of formula I to treat VCAM-1 mediated disorders which include cystic fibrosis. Importantly, Ni et al. teach that the compounds of formula I can be administered in combination with a second biologically active agent wherein such agents include tricyclic antidepressants and amitriptyline. Consequently, the Examiner maintains that one of ordinary skill in the art would have found it obvious to utilize the combination therapy of Ni with amitriptyline or tricyclic antidepressant for the treatment of cystic fibrosis since Ni et al. teach the combination of the aforementioned compounds for the treatment of such disease. As for applicant's arguments that VCAM has not shown to play a role in cystic fibrosis, such arguments are not persuasive as the prior art clearly teaches the combination of amitriptyline or tricyclic antidepressants for the treatment of VCAM disorders including cystic fibrosis. In light of such disclosure and because Ni explicitly teaches the use of formula I in combination with tricyclic anti-depressants to treat VCAM disorders including cystic fibrosis, one of ordinary skill in the art would have indeed found it obvious to try the combination therapy of Ni to treat cystic fibrosis irrespective of the role of VCAM in cystic fibrosis. If however, applicant does not believe that Ni is enabled for the treatment of cystic fibrosis, the burden is on applicant to provide evidence to demonstrate the inoperability of the prior art. *When the*

reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP § 716.07.

As for applicant's arguments that Ni et al. do not teach any compound by inhalation, such arguments are not persuasive as the Examiner maintains that Daines was provided to demonstrate that formulations targeted for the treatment of cystic fibrosis is known in the art to be formulated as inhalation products. Regardless, if Daines teaches leukotriene agonists in the composition, the Examiner submits that Daines was again provided to demonstrate that inhalation formulations for cystic fibrosis are known in the art and formulation of such products would have been within the purview of the skilled artisan especially given that cystic fibrosis is characterized by lung complications and thus medications that deliver drugs directly to the lungs would thus have been beneficial.

As for Chen, it was provided to demonstrate that imipramine and amitriptyline are both tricyclic antidepressants and thus substitution of one for another would have yielded predictable results. Finally, Bilgi was provided to demonstrate that tetracyclic antidepressants are known in the art as more beneficial than tricyclic antidepressants that tend to cause various side effects. In fact, Bilgi et al. teach that administration of

tetracyclic antidepressants led to improve cardiac effects. Thus, to one of ordinary skill in the art would have found it obvious to try tetracyclic antidepressants instead of tricyclic antidepressants since Bilgi et al. teach that tricyclic anti-depressants caused various side effects. Consequently, the Examiner maintains that the rejections of record were indeed proper.

For the foregoing reasons, the rejections of were indeed proper. However, in view of applicant's amendment, the following 112, second paragraph and modified 103 (a) Non-Final rejections are being made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 47-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (**see M.P.E.P 608.01 (k)**).

Claims 47-52 are particularly vague and indefinite given that applicant is claiming a method comprising a formulation comprising a carrier and a pharmaceutically active component consisting essentially of an antidepressant selected from the group consisting of a tricyclic antidepressant and a tetracyclic antidepressant (**in sentences 2-**

4 of claim 47). Specifically, it is unclear to the Examiner what components applicant is trying to include or exclude out of the formulation.

As a result of the above inconsistencies, the aforementioned claims are unable to be examined as disclosed given that the scope of the claimed subject matter would not be able to be determined by one of ordinary skill in the art. However, for the sake of compact prosecution, the Examiner will construe the claim as a "formulation consisting essentially of a carrier and a pharmaceutically active component consisting of an antidepressant selected from the group consisting of tricyclic antidepressant and a tetracyclic antidepressant".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 42, 44-48 and 50-52 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Ni et al. (U.S. 6,608,101 B1, previously cited) in view of Chen et al. (U.S. 6,248,528, B1, previously cited) and in further view of New York Times (December 1997, pgs. 1-3).

As for the term "consisting essentially of" limitation in claim 47 (as interpreted by the Examiner; see rejection under 112, second paragraph), for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d. If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964).

Ni et al. teach compounds of formula I for inhibiting expression of VCAM-1 and useful to treat a patient with a disorder mediated by V-CAM-1 including cystic fibrosis (see abstract, col. 10, lines 5-12, and col. 15, lines 6-9). In fact, Ni et al. teach that VCAM is upregulated in a wide variety of disease states including cystic fibrosis (see col. 43, lines 55-59). Additionally, Ni et al. teach that the compounds of the instant invention (i.e. formula I) can be combined with a carrier and a second biologically active agent to increase the effectiveness against the target disorder (see col. 44, lines 56-61 and col. 165, claim 44). Specifically, Ni et al teach that the present invention can be combined with amitriptyline (instant claims 42, 44-45, 48, and 50-51) or tricyclic-antidepressants (instant claims 42 and 48; see col. 47, lines 32-39 and col. 165, lines 37-38 and 59).

Ni et al. do not teach the use of imipramine as the tricyclic antidepressant in the treatment of cystic fibrosis.

Ni et al. however teach the use of secondary biologically active agents to help in the effectiveness of the disease being treated. Ni et al. further teach the use of amitriptyline and tricyclic anti-depressants as secondary biological active agents to be used in combination with the compound of formula I.

Chen et al. were provided to demonstrate that imipramine and amitriptyline are both tricyclic antidepressants (see col. 21, lines 39-40 and 49-50). As a result, the Examiner maintains that one of ordinary skill in the art at the time of the invention was made would have found it obvious to substitute imipramine for the amitriptyline of Ni et al. given that the substitution of one known element for another would have yielded predictable results.

New York Times teaches an inhalant drug approved for cystic fibrosis (see pg. 1, paragraph 1). Specifically, New York Times teaches that while the drug Tobramycin has been available intravenously, a new version for inhalation was developed due to the nature of cystic fibrosis (see pg. 1, paragraph 2). Cystic fibrosis is a genetic disease where patients die of lung failure due to thick, sticky mucus that clogs the airways and traps bacteria that cause infection (See pg. 1, paragraph 4). While the standard treatment of the drug is intravenous, higher doses typically cannot be given to patients

who lose their lung functions due to its severe side effects (see pg. 1, paragraph 5). As a result, doctors sought ways to deliver the same drugs directly to the lungs wherein direct lung delivery resulted in increased patients' lung function and decreased side effects (see pg. 1, last paragraph and pg. 2, paragraph 3).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the combination therapy composition of formula I and amitryptiline of Ni et al. for the treatment of cystic fibrosis since Ni et al. teach that such combination is effective in treating V-CAM associated disorders such as cystic fibrosis. Similarly, one of ordinary skill in the art would have found it obvious to substitute imipramine for amitriptyline in the aforementioned combination since Chen demonstrated that both imipramine and amitriptyline are known equivalents and would thus be expected to behave similarly. Additionally, one of ordinary skill in the art at the time of the invention would have found it obvious to formulate the composition of Ni et al. as an inhalation composition since the New York times teaches that intravenous formulations for cystic fibrosis are not effective in high doses since they cause severe side effects and thus the motivation to avert such side effects is to formulate such composition as inhalants. Moreover, the Examiner contends that it is well within the purview of the skilled artisan during routine experimentation to formulate the composition in various forms including inhalants since inhalant drug formulations are known in the cystic fibrosis art and to minimize serious side effects when delivering high dosages as taught by the New York Times article. Thus, given the teachings of Ni,

Chen and New York Times, one of ordinary skill in the art would have been motivated to utilize amitryptiline or imipramine in the treatment of cystic fibrosis and further formulate it as an inhalable composition with the reasonable expectation of providing a method efficient in treating cystic fibrosis and a method with reduced side effects.

Claims 43 and 49 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Ni et al. (U.S. 6,608,101 B1, previously cited) in view of Chen et al. (U.S. 6,248,528, B1, previously cited) and in further view of New York Times (December 1997, pgs. 1-3) as applied to claims 40, 42, 44-48 and 50-52 and in further view of Bilgi et al. (Canadian Family Physician. May 1979; Vol. 25, pgs. 619-620, 622, and 624-625, previously submitted).

The Ni, Chen and New York Times references are as discussed above and incorporated by reference herein. However, Ni, Chen and New York Times do not teach the antidepressant as a tetracyclic antidepressant.

Bilgi et al. teach that tricyclic antidepressants (TCA) are effective in treating depressive states but may impose minor therapeutic side effects (se pg. 619, left col.). Indeed, Bilgi et al. teach that treatment with tricyclic antidepressants such as amitriptyline, imipramine, and clomipramine caused various side effects including hypotension, hypertension, arrhythmia, and sinus tachycardia (see pg. 620 and pg. 624, table 1). As for the tetracyclic antidepressant, maprotiline, Bilgi et al. teach that

administration of maprotiline to healthy individuals resulted in minimal ST-T changes which later disappeared despite repeated administration of the compound (see pg. 622, right col., paragraph 1 under maprotiline and its effects Section). In fact, Bilgi et al. teach that treatment with maprotiline can be given safely to cardiac patients as it improves ventricular function, end-diastolic pressure, and stroke work index and further suggest treatments with tetracyclic antidepressants to patients predisposed to cardiotoxicity to TCA (see pg. 622, right col., and pg. 625, Conclusion Section).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the tetracyclic antidepressant of Bilgi et al. instead of the TCA of Ni et al. since Bilgi et al. teach them as equivalent to TCA. Moreover, one of ordinary skill in the art would have found it obvious to utilize tetracyclic antidepressants as opposed to TCA since Bilgi et al. teach that tetracyclics pose minimal side effects and lead to improved ventricular function. Thus, given the teachings of Bilgi et al., one of ordinary skill in the art would have been motivated to substitute tetracyclics for the amitriptyline in the treatment of cystic fibrosis with the reasonable expectation of providing a method efficient in treating cystic fibrosis and a method that entails minimal side effects.

Claims 40, 42, 44-45, 47-48, and 50-51 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Sanders et al. (Am J. Respir. Crit. Care Med., 2000,

Vol. 162, pgs. 1905-1911) in view of Baillie (The Lancet, 1967, pgs. 369-370) and in further view of New York Times (December 1997, pgs. 1-3).

As for the term "consisting essentially of" limitation in claim 47 (as interpreted by the Examiner; see rejection under 112, second paragraph), for the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d. If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. In re De Lajarte, 337 F.2d 870, 143 USPQ 256 (CCPA 1964).

Sanders et al. teach that cystic fibrosis (CF) is characterized by a mutation in the CFTR protein (see pg. 1905, left col..). This protein is located in the exocrine glands and secretory epithelia wherein defects in such protein in the respiratory tract alters the composition of respiratory mucus and lead to respiratory complications in CF (see pg. 1902, left col.). Such complications include airway obstruction, chronic lung infection, and inflammatory reactions (see pg. 1902, left col.). Importantly, Sanders et al. teach that as compared to normal airway secretions, CF mucus has a higher consistency and tends to form a blanket wherein pathogens and harmful particles tend to reside (see pg. 1902, right col.).

Sanders et al. do not teach the use of tricyclic or tetracyclic antidepressants in the treatment of cystic fibrosis.

Baillie teaches the use of amitriptyline and its effect on sputum (i.e. mucus; see pg. 369, right col., bottom paragraph). Specifically, Baillie teaches that 150 mg of amitriptyline daily caused increased viscosity in the sputum (see pg. 369, right col., bottom paragraphs). When the dosage of amitryptiline was halved however (i.e. reduced to 75 mg), there was an increase in fluidity of the sputum and expectoration became easier (see pg. 369, right col., bottom paragraph). As a result of these observations, amitriptyline was prescribed to a fibrocystic disease patient who had chronic chest infection (see pg. 370, let col. paragraph 1).

New York Times teaches an inhalant drug approved for cystic fibrosis (see pg. 1, paragraph 1). Specifically, New York Times teaches that while the drug Tobramycin has been available intravenously, a new version for inhalation was developed due to the nature of cystic fibrosis (see pg. 1, paragraph 2). Cystic fibrosis is a genetic disease where patients die of lung failure due to thick, sticky mucus that clogs the airways and traps bacteria that cause infection (See pg. 1, paragraph 4). While the standard treatment of the drug is intravenous, higher doses typically cannot be given to patients who lose their lung functions due to its severe side effects (see pg. 1, paragraph 5). As a result, doctors sought ways to deliver the same drugs directly to the lungs wherein

direct lung delivery resulted in increased patients' lung function and decreased side effects (see pg. 1, last paragraph and pg. 2, paragraph 3).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the tricyclic antidepressant amitriptyline to treat cystic fibrosis since Sanders teaches that CF is characterized by abnormal mucus that leads to lung infections and in view of Baillie who teaches that amitriptyline was effective in reducing the viscosity of the mucus and consequently the barrier (as taught by Sanders) would no longer reside in the lungs of such patients and infections would thus be reduced and/or prevented. Additionally, one of ordinary skill in the art at the time of the invention would have found it obvious to formulate the composition of Baillie as an inhalation composition since the New York times teaches that intravenous formulations for cystic fibrosis are not effective in high doses since they cause severe side effects and thus the motivation to avert such side effects is to formulate such composition for inhalation. Moreover, the Examiner contends that it is well within the purview of the skilled artisan during routine experimentation to formulate the composition in various forms including inhalants since inhalant drug formulations are known in the cystic fibrosis art and to minimize serious side effects when delivering high dosages as taught by the New York Times article. Thus, given the teachings of Sanders, Baillie, and New York Times, one of ordinary skill in the art would have been motivated to utilize amitryptiline in the treatment of cystic fibrosis and further formulate it as an inhalable composition with the

reasonable expectation of providing a method efficient in treating cystic fibrosis and a method effective in reducing side effects.

Claims 46 and 52 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Sanders et al. (Am J. Respir. Crit. Care Med., 2000, Vol. 162, pgs. 1905-1911) in view of Baillie (The Lancet, 1967, pgs. 369-370) and in further view of New York Times (December 1997, pgs. 1-3) as applied to claims 40, 42, 44-45, 47-48, and 50-51 and in further view of Chen et al. (U.S. 6,248,528, B1, previously cited).

The Sanders, Baillie, and New York Times references are as discussed above and incorporated by reference herein. However, Sanders, Baillie, and New York Times do not teach that the tricyclic antidepressant is imipramine.

Chen et al. is being provided to demonstrate that imipramine and amitriptyline are both tricyclic antidepressants (see col. 21, lines 39-40 and 49-50). As a result, the Examiner maintains that one of ordinary skill in the art at the time of the invention would have found it obvious to substitute imipramine for the amitriptyline of Ni et al. given that the substitution of one known element for another would have yielded predictable results.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to substitute imipramine for amitriptyline in the aforementioned combination since Chen demonstrated that both imipramine and amitriptyline are known equivalents

and would thus be expected to behave similarly. Thus, given the teachings of Sanders, Baillie, New York Times, and Chen, one of ordinary skill in the art would have been motivated to substitute imipramine for amitryptiline in the treatment of cystic fibrosis as taught by Chen with the reasonable expectation of providing a method efficient in treating cystic fibrosis and a method effective in reducing side effects.

Claims 43 and 49 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Sanders et al. (Am J. Respir. Crit. Care Med., 2000, Vol. 162, pgs. 1905-1911) in view of Baillie (The Lancet, 1967, pgs. 369-370) and in further view of New York Times (December 1997, pgs. 1-3) as applied to claims 40, 42, 44-45, 47-48, and 50-51 and in further view of Bilgi et al. (Canadian Family Physician. May 1979; Vol. 25, pgs. 619-620, 622, and 624-625, previously submitted).

The Sanders, Baillie, and New York Times references are as discussed above and incorporated by reference herein. However, Sanders, Baillie, and New York Times do not teach the antidepressant as a tetracyclic antidepressant.

Bilgi et al. teach that tricyclic antidepressants (TCA) are effective in treating depressive states but may impose minor therapeutic side effects (se pg. 619, left col.). Indeed, Bilgi et al. teach that treatment with tricyclic antidepressants such as amitriptyline, imipramine, and clomipramine caused various side effects including hypotension, hypertension, arrhythmia, and sinus tachycardia (see pg. 620 and pg. 624,

table 1). As for the tetracyclic antidepressant, maprotiline, Bilgi et al. teach that administration of maprotiline to healthy individuals resulted in minimal ST-T changes which later disappeared despite repeated administration of the compound (see pg. 622, right col., paragraph 1 under maprotiline and its effects Section). In fact, Bilgi et al. teach that treatment with maprotiline can be given safely to cardiac patients as it improves ventricular function, end-diastolic pressure, and stroke work index and further suggest treatments with tetracyclic antidepressants to patients predisposed to cardiotoxicity to TCA (see pg. 622, right col., and pg. 625, Conclusion Section).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the tetracyclic antidepressant of Bilgi et al. instead of the TCA of Sanders et al. since Bilgi et al. teach them as equivalent to TCA. Moreover, one of ordinary skill in the art would have found it obvious to utilize tetracyclic antidepressants as opposed to TCA since Bilgi et al. teach that tetracyclics pose minimal side effects and lead to improved ventricular function. Thus, given the teachings of Bilgi et al., one of ordinary skill in the art would have been motivated to substitute tetracyclics for the amitriptyline in the treatment of cystic fibrosis with the reasonable expectation of providing a method efficient in treating cystic fibrosis and a method that entails minimal side effects.

Conclusion

No claims are allowed.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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03/17/2010

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